The importance of follow-up forms

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Outline

• Introduction: Follow-up information and its use
• Missing follow-up data: unreported events and “censored” data
• Consequences of (relevant) censoring
• Summary & Your questions
Follow-up information and its use
Follow-up information

- All information on the final outcome, evolution of disease and relevant events
  - Survival status / death (cause)
  - Disease status / relapse / progression
  - Complications (GvHD, infection, ...)
  - Treatments
Follow-up information

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A (hypothetical) survival curve

- Time to death $\rightarrow$ Probability of surviving beyond $t$

Theoretical curve
Failure-free survival curves

- Time to progression or death (composite final outcome)

Real data, estimated curves

NMAM2000 EBMT trial
Prospective comparison auto – allo regimens
Cumulative incidence curves

- Probability of achieving CR within time t (event that may not occur)

NMAM2000 EBMT trial
Prospective comparison auto – allo regimens
Comparison of curves (testing)

- Statistical significance: can the observed difference be due to pure chance?

The “p-value” measures the probability that this happens.

Very small $p$ indicates that the results observed are not “chance” and can be reproduced.
Other useful curves

- E.g.: Probability of surviving in CR

NMAM2000 EBMT trial
Prospective comparison auto – allo regimens
"Missing" Follow-up
Different situations

- (Intermediate) Events are not reported at all
- MISSING info

- The follow-up is incomplete
  - End of study (trial, prospective study) or time of analysis (registry study) too early
  - Patients are lost to follow-up
- INCOMPLETE info
Unreported (intermediate) events

- Especially “secondary” events like GvHD or infection are often unreported
- Consequences: the incidence is underestimated, the probability of survival event-free is overestimated, etc
Incomplete (too short) Follow-up

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The survival time is not *completely unknown*

- For patients alive at last follow-up (e.g. at 16 months) we know that Time To Death is $>16$
  - Patient died at 14 months: $T=14$
  - Patient last-seen-alive at 16 months: $T>16$

- This type of data is called “censored”
- Specific statistical methods manage to incorporate this info when estimating survival curves
A “real” survival curve (with censored data)

- Time to death $\rightarrow$ Probability of surviving beyond $t$
Consequences of censoring
Estimation is less precise

Survival probability at 24 months:
- **green**: 11% (6% - 21%)
- **black**: 28% (14% - 56%)
Over-interpretation of the tail: cured?

Reliability of tails

- complete fup
- huge censoring

months since SCT

black: 50 39 33 26 21 18

green: 50 10 2 2 0 0

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Over-interpretation of the tail: cured?

Group 0 (black) vs. Group 1 (red) (“cured”)
Differences may be less detectable

- Complete f-up
  - \( p = 0.036 \)

- Limited censoring
  - \( p = 0.052 \)
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Differences may be less detectable

Complete f-up

b) Strong censoring

p = 0.036

p = 0.099
Wrong conclusions

Complete f-up

\[ p = 0.257 \]

Early censoring

\[ p = 0.019 \]
Wrong conclusions

Group 0 (black) vs. Group 1 (red) turns from being protective to having higher risk in the long term.

With relevant censoring, it is more difficult to detect statistically the risk effect in the long term; with very early censoring we even miss to observe the crossing.
Bias: systematically wrong conclusions

• Censoring should NOT be related to current and future risk of failure:

• The probability of survival is always overestimated if loss-to-follow-up occurs to patients who have higher risk of death
  – E.g. loss of patients with high toxicity, or of pts who need salvage treatment

• The probability of survival is always underestimated if loss-to-follow-up regards patients with better prognosis
  – E.g. follow-up continues only for pts with co-morbidity / secondary effects / who need treatment
“Confounding” is a source of bias. Example:

- Compare TCD and no-TCD for Survival. TCD looks worse.
- A risk factor X is more present in TCD. Could explain worse Survival of TCD pts. X is a confounder.
Censoring and confounding

• Different censoring in two groups may be related to or act as a confounder.
• One particular case is different censoring between centres.
• E.g.: TCD → One big experienced center, good reporting, good f-up; No-TCD → smaller centers, less resources, poorer reporting & f-up.

(Worse pts go to Big center)
Summary & Questions
Summary

- Un-reported intermediate event → under-estimation of their incidence, over-estimation of failure-free survival, etc.
Summary

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• Poor (short) follow-up, loss-to-f-up $\rightarrow$
  – Unreliable estimates, in particular in the tail (with problem for assessing the fraction of “cured”)
  – Less significant (detectable) differences
  – Misleading pictures and tests, wrong conclusions (in particular with time-varying differences)
  – Bias if related to confounders
• Un-reported intermediate event $\rightarrow$ under-estimation of their incidence, over-estimation of failure-free survival, etc.

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• Loss-to-f-up related to risk of failure $\rightarrow$ systematic estimation error
Your questions

• Problems when the follow up is too short.
• How poor follow up distorts the results of the analyses
• How bias can have serious, harmful implications.
• Problems when the follow up is different across centres (some are very good, some are very poor)
• Assuming good follow up, limits to the predictive power of the analysis: can you extrapolate to x more years?
• Is there a limit (statistically speaking) to how long the follow up needs to be?
• Your input: can reporting follow-up be facilitated? How?
Thank you!!